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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,724	KOVACS ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24 and 46-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24 and 46-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed September 3, 2002. Currently, claims 1-14, 16-24, 46-53 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action contains new grounds of rejection necessitated by amendment.

4. As provided in Rule 1.126, "when claims are added, they must be numbered by the applicant consecutively beginning with the number next following the highest numbered claim previously presented (whether entered or not)." Therefore, newly presented Claims 25-32 have been renumbered 46-53.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-24, 46-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A1) Claims 1-22 are indefinite because it is unclear how one would determine prior to amplification using primers derived from human P. carinii whether the resulting amplified sequence was at least 79% identical with another sequence. Using primers

which are 100% identical with the sequence of SEQ ID NO: 13 would amplify any thing between the two primers. It is unclear how one would ensure that only regions with at least 79% identity between the 100% complementary primers were amplified. Thus, the metes and bounds of the claimed invention are unclear. Claims 1-22 do not require detection of one of the newly identified sequences, but rather merely require as positive process steps methods of using two or more primers where the primers hybridize to the provided sequences and determining whether an amplified sequence is present. Therefore, the claims do not appear to be limited to detecting the newly discovered sequences. It is unclear whether the phrase limits the claim in any way.

B1) Claim 6-7, 47-48 are indefinite over the recitation "approximately the same number of nucleotides" because it is unclear the relationship between the elements of the claims. It is unclear what has approximately the same number of nucleotides, the 15 contiguous nucleotides or a nucleic acid having at least 91% sequence homology. Moreover, approximately is an indefinite term which is relative. Approximately has not been defined in the specification, therefore, the metes and bounds are unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-11, 13, 14, 18-24 and Newly added Claims 46-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garbe et al. (Infection and Immunity, Vol. 62, No. 8, pages 3092-3101, August 1994) in view of Hogan (US Pat 5,595,874, January 1997).

Garbe et al. (herein referred to as Garbe) teaches the molecular characterization of clustered variants of gene encoding major surface antigens of human *Pneumocystis carinii*. Garbe teaches the nucleic acid sequence of one gene and three partial sequences from other genes. Garbe teaches sera from humans was analyzed (page 3093)(limitations of Claim 18). Garbe teaches a protein alignment for the msgI to msgIV and rat msg sequences. Garbe the amino acid sequence between 980-1030 of MsgI and MsgII are highly conserved regions. SEQ ID NO: 19 and 20 are within the region which is conserved between MsgI and MsgII. SEQ ID NO: 17 is 100% identical to the sequence illustrated in Figure 5.

Garbe does not specifically teach detecting *Pneumocystis carinii* using PCR amplification to conserved regions.

However, Hogan et al. (herein referred to as Hogan) teaches the use of specific primers col. 6-7, lines 50-67, lines 1-12, and furthermore provides specific guidance for the selection of primers,

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Hogan teaches labeling the oligonucleotide probe (col 8, lines 65-68)(limitations of Claim 20). As clearly illustrated in Example 1, Hogan teaches using a single stranded oligonucleotide which is labeled to detect the presence of the organism of interest. The oligonucleotide used in the detection assay is specific to the organism and does not cross react with closely related sequences (col 12)(limitations of Claim 23).

Similarly, Example 3, illustrates the detection of a complex of organisms using a labeled probe which is specific to the complex (col 17-18).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have designed probes and primers to conserved regions of the human gpA/MSG genes from human *Pneumocystis* in order to detect MSG protein encoding sequences. The ordinary artisan would have recognized, given the alignment of Garbe, that regions within the two human gpA/MSG genes were conserved between the two genes and would have been motivated to have designed probes and primers to conserved regions as taught by Hogan to enable detection of human gpA/MSG nucleic acid sequences. The ordinary artisan would have been motivated to have detected human MSG encoding nucleic acid sequences because *Pneumocystis* causes pneumocystosis, an AIDS-associated pneumonia, and adverse reactions to chemotherophy. The level of skill in the art for designing primers and probes to known conserved regions between sequences is extremely high. Therefore, the skilled artisan would have used primers, for example, from the region which is highly conserved between the human sequences namely amino acids 980-1030 to amplify the gpA/MSG gene region provided by Stringer. The skilled artisan would have been motivated to have designed primers which flank the conserved regions. These primers would clearly encompass primers comprising SEQ ID NO: 19 and SEQ ID NO: 20 since these primers lie in regions which are conserved between the human MSG gene sequences. With respect to SEQ ID NO: 17, the sequence is 100% identical with a known MSG gene sequence such that using the primer would facilitate detection of the presence of *P. carinii* as required.

Response to Arguments

The response traverses the rejection. The response asserts that the claim has been amended to recite a specific highly conserved region within a human P. carinii nucleic acid which is not taught or suggested in the art. This argument has been reviewed but is not convincing because SEQ ID NO: 5, nucleotides 2845-3090, for example, is 87.6% identical with the nucleic acids of Garbe, namely nucleotides 2999-3244. Therefore, in the event that the claims are directed to specifically detecting a nucleic acid which is at least 79% identical with SEQ ID NO: 5, nucleotides 2845-3090.

Alternatively, as provided in the 112/2nd rejection above, the claim is not clear that the claim requires detection of a nucleic acid which is at least 79% identical with the sequences provided. The active process steps of the claims are directed to using two or more oligonucleotide primers that hybridize to the highly conserved region and determining whether an amplified sequence is present. Therefore, the amplified sequence does not appear to have to be one of the newly identified sequences. Garbe teaches specific regions within the alignment of the protein which are conserved. By comparing the protein alignment to the provided nucleotide sequence, the ordinary artisan would have designed primer in the conserved regions such that all strains of P. carnii may be detected. A comparison between the exemplified primers of the instant application and the regions delineated by Garbe indicate that the regions are overlapping. Therefore, designing primers to the regions of conservation taught in Garbe would necessarily produce an amplified product which may be detected to indicate the presence of P. carinii in a sample, as required by the preamble. Given this

reading of the claim, primers directed to the regions of Garbe would amplify sequences which are less than 79% identical also. Therefore, since the claims are neither limited to specific primer sequences which are not found in known conserved regions and the claims are not limited to detecting the regions of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, the amendment to the claim fails to overcome the art.

With respect to Claims 23, 24, the claims remain broadly drawn to encompass using SEQ ID NO: 19 or 20 which are within conserved regions of Garbe to detect P. carnii. The claims are not limited to detecting the regions of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, the amendment to the claim fails to overcome the art.

Thus for the reasons above and those already of record, the rejection is maintained.

8. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Garbe et al. (Infection and Immunity, Vol. 62, No. 8, pages 3092-3101, August 1994) in view of Hogan (US Pat 5,595,874, January 1997) as applied to Claims 1-11, 13, 14, 18-20, 23-24 and further in view of Mullis et al. (US Pat. 4,683,195, July 1987).

The specification teaches that an Eco RI site was added to the sense primer (SEQ ID NO: 23) and an Xba I site to the antisense primer to facilitate subcloning (SEQ I DNO: 24) (page 24 of specification, lines 27-30).

Garbe nor Hogan specifically teach inserting a restriction site into SEQ ID NO: 23, 24.

However, Mullis teaches primers may be modified to assist the rapid and specific cloning of the mixture of DNAs produced by the amplification reaction. Mullis teaches modification of the same or different restriction sites are incorporated at the 5' ends of the primers to result in restriction sites at the two ends of the amplified products such that the amplified products, when cut, may be easily inserted into plasmid or viral vectors and cloned (col 15, lines 37-45).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the sequence taught by Garbe in view of Hogan for detection of human *P. carinii* with the teachings of Mullis to introduce known restriction sites into the primer to facilitate subsequent cloning. The ordinary artisan would have been motivated to have inserted known restriction sites into probes and primers designed for detection of *P. carinii* for the express benefit taught by Mullis for subsequent cloning.

Conclusion

9. No Claims Allowable.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
November 14, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600